Abstract: Neither lesions of orbital frontal (OFC) areas 11/13 nor selective amygdala lesions alter the ability to learn stimulus-reinforcer association and reversal discriminations in adult monkeys. Here, we investigated whether the same conclusion will hold true when the same lesions occur in infancy. Infant rhesus monkeys received sham-operations, neurotoxic amygdala lesions, or aspiration OFC 11/13 lesions at 8-10 days of age and were trained on object discrimination reversal (ODR) tasks. Performance on a single pair (1-pair) ODR was assessed at the age of 3 months and 3 years, and then animals were tested in a 5-pairs ODR task in which they had to concurrently learn and reverse five discrimination problems. The results indicated that the ability to solve a single-pair discrimination problem followed by six reversals appears to be late maturing in monkeys but is spared following selective lesions of either OFC areas 11/13 or amygdala, even with the use of the more challenging 5-object ODR task. Finally, performance in the 1-pair ODR at 3 years was comparable to that following adult-onset lesions, indicating that neither OFC areas 11/13 nor amygdala are critical for the development of reversal learning.
September 20, 2011

Dr. Blakemore
Professor of Cognitive Neuroscience
University College London
E-mail: s.blakemore@ucl.ac.uk

Dear Dr. Blakemore,

We would like to submit a manuscript entitled, “Preserved stimulus-reward and reversal learning after selective neonatal orbital frontal areas 11/13 or amygdala lesions in monkeys” to be considered for publication as a Research Report in the journal, Developmental Cognitive Neuroscience.

In this paper, we examined the normal maturation of behavioral flexibility as assessed by the object discrimination reversal paradigm as well as the effects of neonatal selective ibotenic acid lesions of the amygdala, or selective lesions of areas 11 and 13 of the orbital frontal cortex (OFC) on this function. We found that 3-month-old infant monkeys were retarded in learning stimulus-reward associations and reversal learning. However, neither neonatal damage to the amygdala nor neonatal damage to OFC subfields 11 and 13 resulted in significant impairments in reversal learning abilities. The results indicate that, despite severe affective processing impairments found in the same monkeys, these areas are not critical for reversal learning even throughout development. Given the recent upsurge of interest in amygdala and OFC contributions to the neuropathology of many clinical developmental disorders associated with behavioral inflexibility, these findings shed further light on neural structures mediating reversal learning abilities.

The research described in the following manuscript was conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996) and formal approval to conduct these experiments was obtained from both the Animal Care and Use Committees of the University of Texas Health Science Center, Houston as well as Emory University and Yerkes National Primate Research Center. Furthermore, all efforts were made to minimize the number of animals used and their suffering.
Both Dr. Bachevalier and I contributed significantly to this work and have agreed to submission of the manuscript in its present form. These data have been presented in poster sessions of The Society for Neuroscience Annual Meetings in 2007 and 2008, but are not under consideration for publication elsewhere. Neither Dr. Bachevalier nor I have any conflicts of interest in the conduct or reporting of this research.

Thank you for your consideration.

Sincerely,

Andy M. Kazama

List of Authors:

Dr. Andy M. Kazama
Post-Doctoral Fellow
Department of Developmental Cognitive Neuroscience
Yerkes National Primate Research Center
Emory University
954 Gatewood Road
Atlanta, GA 30329
e-mail: akazama@emory.edu

Dr. Jocelyne Bachevalier
Professor of Psychology
Yerkes National Primate Research Center
Emory University
954 Gatewood Road
Atlanta, GA 30329
Phone #: 404-727-9765
e-mail: jbachev@emory.edu
Dear Dr. Blakemore,

We would like to submit the following minor revisions to the manuscript (DCN-D-11-00101) entitled “Preserved stimulus-reward and reversal learning after selective neonatal orbital frontal areas 11/13 or amygdala lesions in monkeys” to be considered for publication in *Developmental Cognitive Neuroscience*. The revisions are described below. Thank you for your valuable time.

Best,

Andy M. Kazama & Jocelyne Bachevalier

Reviewer #1: Preserved stimulus-reward and reversal learning after selective neonatal orbital frontal areas 11/13 or amygdala lesions in monkeys

Kazama and Bachevalier, 2011 - Developmental Cognitive Neuroscience

The author’s revisions, especially the rewriting of the results section, have significantly improved quality of the manuscript. I only have a few comments.

1) Lesion extent. a) If a ventral view of one of the neonatal lesions is available please include it in the present manuscript. Furthermore showing the correspondence between MRI and the ventral view would help strengthen the manuscript. b) If time and resources permit, a high resolution scan of the neonatal lesions would be really helpful, however, only include if simple to do so.

   a. *We believe that an additional ventral view to the current coronal sections through the extent of the OFC lesions (see Figure 1) will not provide more information than the detailed estimate of the lesions we gave for each case on Table 1. So we have opted for not including this ventral view.*

2) Response to reviewer 1, comment 5 (comparison of neonatal and adult lesions). The authors make a strong case that neither neonatal nor adult OFC lesions affect the ability of monkeys to perform object reversal learning. A recent study by Walton et al., Neuron (2010) reported the opposite. In this report it was found that the lateral OFC, corresponding to areas 11 and 13, is important for reversals and learning the contingency between stimuli and rewards. A few sentences commenting on the difference in findings between this and the present study should be added to the discussion.
a. After considering Walton et al (Neuron, 2010), it is interesting to note from the illustrations of their OFC lesions (see Figure 1) that the lesions were not restricted to areas 11/13, as in the present paper, but included in addition the most medial sector (area 14). So, it is not surprising to see that these authors have found a deficit in reversal learning similar to that already reported in previous studies (Izquierdo et al., 2004; Kazama and Bachevalier, 2009). We have thus added this reference in the discussion when we compared the extent of OFC lesions on ODR performance.

3) I would like to thank the authors for re-analysing the data using non-parametric methods. To ward off similar comments the authors may want to include a sentence in the results section stating that non-parametric analyses were consistent with t-tests.

a. We have added this to the Data Analysis section of the Methods.

Reviewer #3: The authors have answered all of my queries well and the paper seems more rigorous in its revised form.

The one minor comment is that there is still some inconsistencies in the way the statistics are reported. For instance, non-significant statistics are sometimes reported as "NS" (e.g., p16), sometimes as "p>0.05" (e.g., p17) and sometimes as the exact statistics (e.g., p18). I would prefer full stats in all cases - i.e., p = X or p > X, will go with whatever the journal's policy is on this matter.

a. We have corrected all inconsistencies.
HIGHLIGHTS

- We examined reversal learning in monkeys at two time-points (3-months and 3-years)
- Reversal learning follows a protracted development
- The amygdala is not necessary to develop normal reversal learning abilities
- Areas 11/13 of the OFC are not necessary for developing reversal learning abilities
Preserved stimulus-reward and reversal learning after selective neonatal orbital frontal areas 11/13 or amygdala lesions in monkeys.

Andy Kazama and Jocelyne Bachevalier

Department of Psychology and Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA

Correspondence to: Jocelyne Bachevalier, Yerkes National Primate Research Center, Emory University, 954 Gatewood Road, Atlanta, GA 30329, Phone: 404-727-9765, Fax: 404-727-8088, Email: jbachev@emory.edu

Abbreviated Title: Reversal learning after neonatal orbital frontal and amygdala lesions.

Keywords: Reward, Decision, Prefrontal, Amygdala, Response Inhibition, Development
ABSTRACT:

Neither lesions of orbital frontal (OFC) areas 11/13 nor selective amygdala lesions alter the ability to learn stimulus-reinforcer association and reversal discriminations in adult monkeys. Here, we investigated whether the same conclusion will hold true when the same lesions occur in infancy. Infant rhesus monkeys received sham-operations, neurotoxic amygdala lesions, or aspiration OFC 11/13 lesions at 8-10 days of age and were trained on object discrimination reversal (ODR) tasks. Performance on a single pair (1-pair) ODR was assessed at the age of 3 months and 3 years, and then animals were tested in a 5-pairs ODR task in which they had to concurrently learn and reverse five discrimination problems. The results indicated that the ability to solve a single-pair discrimination problem followed by six reversals appears to be late maturing in monkeys but is spared following selective lesions of either OFC areas 11/13 or amygdala, even with the use of the more challenging 5-object ODR task. Finally, performance in the 1-pair ODR at 3 years was comparable to that following adult-onset lesions, indicating that neither OFC areas 11/13 nor amygdala are critical for the development of reversal learning.
1. INTRODUCTION

Damage to the orbital frontal cortex (OFC) has been associated with cognitive and behavioral inflexibility (Mishkin, 1964; Jones and Mishkin, 1972), often demonstrated by deficits in reversal learning in a variety of species, including rodents (Bissonette et al., 2005; Chudasawa and Robbins, 2003; Schoenbaum et al., 2002, 2003), monkeys (Butter, 1969; Dias et al., 1996; Izquierdo et al., 2004; Meunier et al., 1997; Mishkin, 1964), and humans (Bechara et al., 1997; Fellow and Farah, 2003; Hornak et al., 2004). Such deficits are characterized by an inability to adapt responding following changes in stimulus-reward contingencies. The role of the OFC in reversal learning has also been confirmed by electrophysiological recording studies demonstrating that the activity of OFC neurons changes with alterations in the reward contingencies (Holland and Gallagher, 2004; Rolls et al., 1996; Schoenbaum et al., 1998; Thorpe et al., 1983; Tremblay and Schultz, 1999; Paton et al., 2006; Morrison and Salzman, 2009; Morrison et al., 2011). Nevertheless, more recent lesion studies in monkeys have shown that not all OFC subregions are critical for this function. OFC lesions restricted to either OFC areas 11/13 or area 14 spared object reversal learning (Kazama and Bachevalier, 2009; Rudebeck and Murray, 2011). Thus, the data suggest that the object reversal deficit reported in the earlier lesion studies could be attributed to damage encompassing several OFC subfields and/or to selective damage to ventrolateral prefrontal area 12 (Butter, 1969; Dias et al., 1996; Iversen and Mishkin, 1970; Rygula et al., 2010).

A similar pattern of results emerged when considering the contribution of the amygdala to object reversal learning. Given the extensive connections linking the OFC and the amygdala (Amaral and Price, 1984; Barbas, 2007; Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007),
it is not surprising that object reversal learning deficits have also been reported after damage to the amygdala (Aggleton and Passingham, 1981; Barrett, 1969; Jones and Mishkin, 1972; Schoebaum et al., 2003; Schwartzbaum and Poulos, 1965; Spiegler and Mishkin, 1981). But again, this deficit follows electrolytic or aspiration lesions of the amygdala, but not neurotoxic lesions that spared fibers from medial temporal cortical areas coursing through and around the amygdala (Izquierdo and Murray, 2007; Kazama and Bachevalier, 2009). The recent demonstration that direct damage to rhinal cortical areas, sparing the amygdala, yield significant reversal learning impairment (Murray et al., 1998), confirmed that transection of these cortical fibers during aspiration amygdala lesions rather than direct damage to amygdala neurons is the source of the reversal deficits.

Given that neither the OFC fields 11/13 and 14 nor the amygdala are critical for choices guided by changes in reward contingency, it is becoming essential to re-examine the source of object reversal learning deficits reported after early-onset OFC and amygdala damage. Studies in monkeys have shown that performance on object discrimination reversal is impaired by neonatal OFC lesions incurred at 1, 4, or 8 weeks of age (Goldman et al., 1970, 1983; Miller et al., 1973). However, as in the early studies of adult-onset OFC lesions, the damage was extensive, including several OFC subfields (11, 12, 13, and 14). Furthermore, although there exist no studies that have investigated the effects of early-onset amygdala damage on object reversal learning abilities in monkeys, deficits in flexible adaptation to changes in stimulus-contingency have been reported in two human cases with focal developmental amygdala lesions due to Urbach-Wiethe disease (Hampton et al., 2007). Given that in one of the two cases (SM) the damage included fibers around the amygdala and the entorhinal cortex and that both cases had calcification of the amygdala that likely have also altered fibers-en-passage, it is possible
that the object reversal deficit may be more related to damage to the temporal cortical fibers rather than to the amygdala per se.

Thus, the goal of the present study was to determine the effects of selective neonatal damage to OFC areas 11/13 and of neonatal neurotoxic lesions of the amygdala on object reversal learning in monkeys. Infant rhesus macaques received their lesions in the second week of life and were tested on the reversal task at 3 months of age. To assess any possibility of functional recovery with further maturation, the same animals were re-tested on the task when they reached 3 years of age. Preliminary reports of these data have appeared earlier (Bachevalier et al., 2011; Kazama et al., 2002, 2008).

2. METHODS

2.1 Subjects

Twenty-two rhesus macaques (Macaca mulatta) of both sexes (10 males, 12 females) were divided into four groups. Six animals were sham-operated controls and four served as unoperated controls (Neo-N/C), 6 animals received neonatal aspiration lesions of orbital frontal areas 11 and 13 (Group Neo-Oasp), and 6 others received neonatal neurotoxic amygdala lesions (Group Neo-Aibo). An extensive description of the rearing of the animals has been previously described by Goursaud and Bachevalier (2007), and only a brief description is given below.

All animals were housed in individual cages, but given extensive social contact with both peers as well as their human caregivers. At one year of age, they were moved into large enclosure that could accommodate four animals that remained socially housed 24 hrs per day. They were maintained on a 12 hour light/dark cycle, and fed age appropriate diets, consisting of Similac (SMA with Iron) from 0-3 months, which was supplemented with banana-flavored
pellets (PJ Noyes, Cleveland, OH), Purina primate chow (Purina, St. Louis, MI) and fresh fruit from 3-12 months. Purina primate chow (Purina, St. Louis, MI) supplemented with fresh fruit was provided after 12 months. Water was given *ad libitum* from three months of age to adulthood.

For behavioral testing at 3 months, infant monkeys were tested in the morning and received their food ration immediately after testing and another later in the afternoon, providing 12 hours between the last feeding time and behavioral testing to insure motivation. In adulthood, daily food intake was minimally restricted to ensure that the animal remained motivated to retrieve food rewards. All animals received additional testing at different time points after the surgical procedures and prior to being tested in the ODR tasks. This additional testing included measures of object recognition memory assessed with the visual paired-comparison task at 1.5, 6 and 18 months (Zeamer et al., 2010), emotional reactivity (Human Intruder task) at 2 and 5 months (Raper et al., 2009, 2010), attachment to caregivers at 9 months (Goursaud and Bachevalier, 2007), and dyadic social interactions at 3, 6, and 36 months. Between ODR testing at 3 months and 3 years, animals were given the object and spatial paired comparison tasks as well as assessments of emotional reactivity and social interactions at different time points, but no problem-solving tasks were given during this period.

All procedures were approved by the Animal Care and Use Committee of the University of Texas Health Science Center, Houston and of Emory University, and were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. Neuroimaging and surgical procedures were performed when the infants were between 10-15 days of age and were previously described in details (Goursaud and Bachevalier, 2007), and are summarized below.
2.2 Magnetic Resonance Imaging

MRI procedures were performed under gas anesthesia (isoflurane 1.0 – 2.0%, v/v). An intravenous drip solution (0.45% NaCl) maintained hydration, and monitoring of heart rate, respiration rate, blood pressure, body temperature, and expired CO2 was implemented throughout the entire procedure. The animal’s head was secured into a non-ferromagnetic stereotaxic apparatus (Crist Instrument, Damascus, MD) and centered within the scanner bore (GE Signa 1.5 Tesla Echo Speed scanner, GE Medical Systems, Milwaukee, WI). Two MRI sessions (just prior to surgery and then 7 -10 days post-surgery) were given to animals of Groups Neo-Oasp and Neo-Aibo except those in Group Neo-C that received only the pre-surgical MRI session and those in Group Neo-N that served as normal controls. During each session, two series of coronal images were taken through the entire brain using a 3” surface coil: a T1-weighted structural (spin echo sequence, echo time (TE) = 11 ms, repetition time (TR) = 450 ms, contiguous 4 mm sections, 12 cm field of view (FOV), 256 x 256 matrix) and three Fluid Attenuated Inversion Recovery scans (FLAIR, 3 mm thick, each offset by 1 mm; TE = 140 ms, TR = 10,000 ms, inversion time (TI) = 2200 ms, 90° flip angle, contiguous 3 mm sections, 14 cm FOV, 256 x 256 matrix). The pre-surgical T1-weighted images were used either to derive the stereotaxic coordinates for each injection site (Saunders et al., 1990) for animals in Group Neo-Aibo or to localize the orbital frontal sulci and determine the extent of orbital frontal areas 11 and 13 for Group Neo-Oasp (Machado and Bachevalier, 2006, 2007a, b). Post-surgical FLAIR images were compared to matched pre-surgical FLAIR and T1-weighted images to accurately identify localized areas of edema indicative of neurotoxin-induced cell death, and were therefore used to quantify the extent of lesion for all animals in Group Neo-Aibo (Málková et al., 2001;
Nemanic et al., 2002). Post-surgical T1-weighted images were compared to matched pre-
surgical T1-weighted images to identify the location and quantify the extent of orbital frontal
cortex aspiration lesions (Group Neo-Oasp).

2.3 Surgical Procedures

Immediately following the pre-surgery scanning sessions, the animals remained anesthetized
and were brought to the surgical suite where they were prepared for aseptic surgical procedures.
An intravenous drip of 0.45% sodium chloride was used for hydration, vital signs (heart rate,
respiration rate, body temperature and expired CO$_2$) were continuously monitored, and a warm
air blanket attached to a Bair hugger® and placed around the animal prevented hypothermia.
Animals in Group Neo-Aibo remained in the stereotaxic apparatus, whereas those in Group Neo-
Oasp had their head secured into a head holder, which permitted free rotation of the animal’s
head during surgery. The animal’s head was then shaved, disinfected with Nolvasan solution
and a local anesthetic (Marcaine, 25%, 1.5m., s.c.) was injected under the skin along the incision
line. The skin and connective tissue were incised and gently retracted. Each group then
underwent lesion-specific procedures.

Orbital Frontal Cortex Lesion: Orbital frontal cortex lesions were intended to damage the
middle sector of the orbital frontal surface, including areas 11 and 13 (Amaral et al., 1992;
Barbas, 2007; Price, 2007). Given the individual variations in the shape and length of the orbital
sulci, pre-surgical T1-weighted MR images were used to reconstruct the ventral surface of the
frontal lobe for each animal. The boundaries of areas 11 and 13 on the ventral surface of the
frontal lobe were defined as (1) a line joining the anterior tips of the medial and lateral orbital
sulci, anteriorly, (2) a line joining the medial bank of the lateral orbital sulcus to the olfactory
striata just anterior to its division into the medial and lateral olfactory tracts, posteriorly, (3) the lateral border of the olfactory stria, medially, and (4) the medial bank of the lateral orbital sulcus, laterally. These borders approximate the extent of areas 11 and 13 in the macaque monkey (see intended lesions, Figure 1, left).

The bone above the supra-orbital ridge was opened and eroded, the dura was cut and retracted, and the brain was gently elevated to gain a full view of the orbital frontal surface. With the aid of a surgical microscope, the lateral and medial orbital sulci and the olfactory stria were visualized and 21- and 23-gauge aspirating probes in combination with electro-cautery were used to gently aspirate the cortical layers until the white matter beneath the cortical mantle could be seen. Special care was used to avoid damaging the white matter.

Neurotoxic amygdala lesion: Using the pre-surgical T1-weighted MR images, the coordinates of 4-6 injection sites were selected within each amygdala to damage all amygdaloid nuclei. Two small craniotomies were performed to expose the brain just above the injection sites and small slits in the dura permitted the needle of a 10 μl Hamilton syringe, held by a Kopf electrode manipulator (David Kopf Instruments, Tujunga, CA), to be lowered to the appropriate injection coordinates. Two Hamilton syringes were filled with ibotenic acid (Biosearch Technologies, Novato, CA, 10 mg/ml in phosphate buffered saline, pH 7.0-7.4) and used to inject 0.2 – 0.6 μl ibotenic acid to each site at a rate of 0.2 μl/min (totaling 0.8-1.6μl of ibotenic acid per amygdala).

Sham lesions: For sham lesions, bilateral craniotomies (similar to those used for amygdala lesions) were made as described above. The dura was cut but no needle penetrations occurred.
Following all surgical procedures, tissues were closed in anatomical layers, the animal was removed from Isoflurane gas and recovered in the surgical facility until it could breathe on its own and maintain an SPO$_2$ of $>88\%$ for 1 h. Beginning 12 h prior to surgery and continuing until one week after surgery, all animals were treated with dexamethasone sodium phosphate (0.4 mg/kg, i.m.) and Cephazolin (25 mg/kg, i.m.) to prevent excessive immunoreactivity and protect against infection, respectively. Acetaminophen (10 mg/kg, p.o.) was given for post-operative pain management.

2.4 Lesion Assessment

MRI Lesion Assessment: For all animals in Group Neo-Aibo, pre-surgical T1-weighted 1 mm coronal images and pre- and post-surgical FLAIR 1-mm coronal images were matched with drawings of 1-mm coronal sections from a normal 2-week-old infant rhesus monkey template brain (J. Bachevalier, unpublished atlas). Hypersignals identified on FLAIR MR images were plotted onto corresponding drawings of the normal brain and these images were then imported into a Java-based image analysis program (ImageJ®; http://rsb.info.nih.gov/ij/) to measure the surface area (in pixels$^2$) of damage for intended targets, as well as all adjacent areas (entorhinal and perirhinal cortex and hippocampus) that may have sustained inadvertent damage. For any given region of interest (ROI), the surface area of hypersignals on each section through each hemisphere was summed and then multiplied by image thickness (1 mm) to calculate a total volume of damage (Gundersen and Jensen, 1987). For each ROI, the volume of damage for each hemisphere was then divided by the volume of that ROI in the normal brain atlas to indicate a percent of the total volume damaged.
For animals in Group Neo-Oasp, pre- and post-surgical T1-weighted 1 mm coronal images were matched to corresponding drawings from the normal infant rhesus monkey atlas. The extent of orbital frontal tissue damaged found on all post-surgery T1-weighted images were plotted onto the corresponding drawings of the normal brain and extent of tissue aspirated from the orbital frontal areas 11 and 13, as well as inadvertent damage to adjacent cortical areas (10, 12, 14, 25 and ia) were measured as described above.

2.5 Behavioral Testing:

Behavioral testing on the 1-Pair ODR at 3 months was performed at the University of Texas Health Science Center at Houston, whereas behavioral testing on the 1-Pair and 5-Pair ODR at 3 years was performed after the animals had been moved to the Yerkes National Primate Research Center. Behavioral testing and testing equipment were the same in the two institutions.

Apparatus and Stimuli: Animals were trained and tested in a reduced version of an adult Wisconsin General Testing Apparatus (WGTA) at 3-months of age, and with the standard adult WGTA at 3-years of age. At both ages, the WGTAs were located in a darkened room containing a white noise generator to mask external sounds. Each WGTA was equipped with a tray containing three food wells (2 cm in diameter, 1 cm deep and 10 or 13 cm apart center to center for infant and adult WGTAs, respectively). Only the two lateral wells were used to hide food rewards, i.e. Bioserve 150g banana-flavored pellets (Bioserve, Frenchtown, NJ), M&M (Mars Inc., McLean, VA) or raisin (Sun-Maid Growers of California, Kingsburg, CA), under three-dimensional objects varying in color, shape and texture. Novel stimuli were used at each age.

A Single-Pair Object Discrimination Reversal (1-Pair-ODR) task was first given at 3 months of age and was repeated at 3 years of age. In addition, at 3 years of age, a 5-Pair Object
Discrimination Reversal (5-Pair-ODR) Task was given immediately after completion of the 1-Pair-ODR task.

**1-pair-ODR:** In this task (Jones and Mishkin, 1972), two objects formed a single discrimination problem. Animals had first to learn which of the two objects was associated with the food reward (Acquisition phase), followed by 6 reversals. During the first trial of the acquisition phase, both objects covered a food reward and the object selected by the animal became the rewarded object (S⁺) for the remaining trials of the phase. Left/right positions of the S⁺ varied according to a pseudorandom sequence (Gellerman, 1933). Animals were given a total of 30 trials per day at 5-sec intertrial intervals until they reached a criterion of 28 correct choices over 30 trials (> 90%) on one day followed by a criterion of 24 correct choices in 30 trials (> 80%) on the next day. Upon reaching this criterion, the reward contingency was switched so that the S⁺ became S⁻ and vice-versa. The animal was again given 30 trials per day until the same criterion was met, after which the reward contingency was switched again. During acquisition phase and reversals, incorrect choices were corrected by re-running the erroneous trial with the S⁺ covering the reward and the S⁻ placed beside the empty well. This forced correction was repeated as many times as necessary until the animals displaced the S⁺. The number of times a trial was repeated served as a measure of perseverative errors.

**5-pair ODR:** The 5-pair ODR task was nearly identical to the 1-pair ODR, but consisted of five concurrent discrimination problems as opposed to one. Ten novel objects were selected to form 5 pairs with only one object serving as the S⁺ in each pair. Again, the S⁺ for each pair was selected on the first 5 trials when both objects of the pairs covered a reward. A total of 40 trials were given per day so that each pair was repeated eight times within a daily session in a pseudo-random order. Similar to the 1-pair ODR, the 5-pair ODR consisted of an acquisition
phase followed by six reversals. Criterion was set at 37 correct choices in 40 trials (> 90%) in one day followed by 34 correct choices in 40 trials (> 85%) in the next day. Forced correction trials identical to 1-pair ODR were given when the S+ objects were not selected in a given trial.

Finally, to assess whether performance after early-onset lesions for both the 1-Pair-ODR and the 5-Pair ODR tasks (Groups Neo-C/N, Neo-Oasp, Neo-Aibo) differed from that of adult-onset lesions, we compared the scores the monkey obtained at 3 years in both tasks with those of adult monkeys that had received the same lesions when they were 3.5 years of age and were tested on both tasks at the age of 4.5 years (Groups C, O, and Aibo from Kazama and Bachevalier, 2009). Similarly to the animals with early-onset lesions, the adult animals had received testing prior to ODR task, which included object recognition memory (visual-paired comparison task), emotional reactivity, social interactions and reinforcer devaluation task.

**Data Analysis**

All statistical analyses were performed using SPSS v. 15. To assess development of ODR performance on intact animals, scores of animals in Group Neo-C/N were first analyzed.

Because case Neo-N-6 was tested only at 3 months and did not receive the 1-pair-ODR and 5-pair-ODR at 3 years, his scores were not included in the statistical analyses. Paired student t-tests were used to compare acquisition errors, and total reversal and perseverative errors on the 1-Pair-ODR at 3 months and 3 years (N = 5) and on both the 1-Pair-ODR and 5-Pair-ODR at 3 years (N = 9). Repeated measure ANOVAs (with Huynh-Feldt corrections when data violated Mauchly’s Sphericity tests) were also used to compare (a) Age and Reversal effects between 3 months and 3 years for the 1-Pair-ODR, and (b) Tasks and Reversal effects between 1-pair and 5-pair-ODR at 3 years. Post-hoc comparisons were performed using Bonferroni corrected
planned t-tests. Comparisons of performance of the 9 animals tested at 3 years with that of six 4-year-old animals tested in the same way (Kazama and Bachevalier, 2009) were also performed on the two tasks separately using t-tests to analyze acquisition errors, total reversal and perseverative errors, and repeated measure Age X Reversal ANOVAs (Huynh-Feldt corrected) to compare reversal and perseverative errors across the six reversals.

To assess the effects of early damage to either the amygdala or OFC areas 11 and 13, acquisition errors and total reversal and perseverative errors were analyzed using repeated measure Group (Neo-C/N, Neo-Oasp, Neo-Aibo) by Age (3 months, 3 years) ANOVA for the 1-Pair-ODR. To further investigate the effects of lesions across the 6 reversals, repeated measure Group (3) X Age (2) X Reversal (6) ANOVAs (Huynh-Feldt corrected) were used to analyze reversal and perseverative errors from 3-months and 3-years on the 1-pair-ODR and Group (3) X Reversal (6) to analyze reversal and perseverative errors on the 5-Pair ODR.

In addition, we tested the effects of early versus late lesions. For each task separately, each lesion group was compared to their matched control using a Group (2) X Age at Lesion (2) ANOVAs for acquisition errors, total reversal and perseverative errors and repeated measure Group (2) X Age at Lesion (2) X Reversals (6) ANOVAs (Huynh-Feldt corrected) for reversal and perseverative errors across the 6 reversals. Significant main effects of group were investigated further using one-sided Dunnett’s tests to investigate differences between Group C/N and each of the lesion groups and significant Group X Reversal interactions or Group X Age at Lesion X Reversal were investigated with Bonferroni corrected two-tailed paired-sample t tests. Because of some individual variations in each group, homogeneity of variances was assessed with Levene’s test for equality of error variance between groups. If Levene’s test was significant, corrected “p” values were used for post-hoc group comparisons. In cases where a
significant Levene’s test was observed, we also conducted non-parametric post hoc Mann-Whitney U tests. Both parametric and non-parametric post hoc tests were consistent, thus only the parametric results are reported below.

Finally, Pearson product moment correlation matrices were used to compare extent of lesion for groups Neo-Aibo and Neo-Oasp with reversal errors and perseverative errors. All unintended damage to surrounding areas > 5% per area was included in the analysis.

RESULTS

3.1 Lesion Extent

The extent of lesion based on MR images has been described in detail in previous reports (see Goursaud and Bachevalier, 2007). Tables 1 and 2 summarize the extent of intended and unintended damage for each animal of Groups Neo-Oasp and Neo-Aibo, respectively. The weighted average (W%; Hodos and Bobko, 1984) was calculated to determine whether damage was highly unilateral (W% < 25%) or particularly extensive and bilaterally symmetrical (W% > 50%).

Group Neo-Oasp: The extent of bilateral OFC damage for Group Neo-Oasp was complete, symmetrical, and averaged 87.1% for areas 11 and 13 (see Table 1 and Figure 1 for illustration of a representative case). In all cases, the lesions also included bilaterally, the anterior portion of the insular agranular area (Ia, 54.1%), the lateral area 12 (14.3%), and the medial area 14 (12.3%).

Group Neo-Aibo: The extent of bilateral amygdala damage in all cases averaged 62.5% (see Table 2 and Figure 2 for illustration of a representative case), and included the central, medial, accessory basal, and dorsal areas of the basal nuclei in all cases, with the majority of
sparing located in the ventral portions of the lateral and basolateral nuclei. For three cases (Neo-Aibo -1, -4, and -6), the damage was substantial and symmetrical (from 63.8% to 76% bilaterally) and for the remaining three cases (Neo-Aibo -2, -3, and -5), the damage was more substantial on the right hemisphere (61.1% to 77.6%) than on the left hemisphere (33.0% to 42.0%). Finally, extent of unintended damage to the perirhinal and entorhinal cortical areas, anterior portion of the hippocampus, and tail of the putamen were negligible for all cases.

3.2 Developmental of ODR performance in control animals:

We first compared performance of the five control animals that were tested at the two ages (3 months vs 3 years) in the 1-Pair-ODR (see Group C/N, Tables 3 and 4). The number of errors during acquisition (Fig. 3A) and the total reversal and perseverative errors significantly dropped with age \([t = 2.82, p < .05; t = 5.341, p < .001, t = 2.69, p < .05, \text{ respectively}]\). The repeated measure Age X Reversal ANOVA for reversal errors (Fig. 3B) revealed a significant main effect of Age \([F (1, 8) = 16.02, p < .005]\) but not of Reversals \([F_{\text{Huynh-Feldt}}(2.22, 17.77) = 1.29, p > .05]\) and no significant Age X Reversal interaction \([F_{\text{Huynh-Feldt}}(2.22, 17.77) = 0.387, p > .05]\). The same analyses for perseverative errors (Fig. 3C) revealed no Age effect \([F(1, 8) = 3.80, p > .05]\) and no Age X Reversal interaction: \(F_{\text{Huynh-Feldt}}(2.36, 18.9) = .244, p > .05\), and the Reversal effect was short of significance \([F_{\text{Huynh-Feldt}}(2.36, 18.90) = 2.85, p = .08]\). Thus, the data indicated improvement of performance with age on both the initial acquisition of the discrimination problem as well as on reversal performance across all six reversals.

Because this improvement in performance with age could reflect not only the impact of brain maturation on cognitive ability but also the influence of successive testing on the same task, we compared performance of the 5 animals in Group Neo-C/N that were tested at 3 years
with that of 4 control monkeys (see Neo-C2, Neo-C4, Neo-C6, Neo-N4, see Table 4) that
received the 1-Pair-ODR task for the first time at 3 years of age. Performance of these two
groups of control animals did not differ for number of errors during acquisition \( (t = .533, p > .05) \) and for both total reversal errors \( [t = .344, p > .05] \) and total perseverative errors \( [t = .445, ps > .05] \). Finally, a repeated measure Group X Reversal on the number of reversal errors
indicated no effects of Group \( [F(1, 7) = .099, p > .05] \), of reversal \( [F_{\text{Huynh-Feldt}}(4.2, 29.4) = 1.52, p > .05] \), and no significant interaction \( [F_{\text{Huynh-Feldt}}(4.2, 29.4) = 1.66, p > .05] \).

Finally, to examine whether performance of 3-year-old monkeys had already reached
adult levels of proficiency, the scores of all 9 control animals tested at 3 years on the 1- and 5-
Pair-ODR were compared to six 4-year-old animals that had been previously tested in the same
ODR tasks (Kazama and Bachevalier, 2009). For the 1-Pair-ODR (Fig. 4 A-C), the 3-year-olds
learned as rapidly as the 4-year-olds [acquisition errors: \( t = 1.56, p > .05 \)]. Yet, they still made
slightly, but significantly, more total reversal errors \( [t = 3.33, p < .01; \text{total perseverative errors}
was not significant: \( t = .003, p > .05 \)] than the 4-year-olds. In addition, a repeated measure Age
X Reversal ANOVA for reversal errors revealed a significant Age effect \( [F(1, 13) = 7.55, p < .02] \) and Reversal effect \( [F_{\text{Huynh-Feldt}}(3.37, 43.82) = 2.80, p < .05] \), but no interaction \( [F_{\text{Huynh-Feldt}}(3.37, 43.82) = 1.03, p > .05] \), indicating that in both group reversal errors slightly decreased
from Reversal 1 to Reversal 6. The same analysis for perseverative errors indicated no Age
effect \( [F(1, 13) = .00; p > .05] \), a significant reversal effect \( [F_{\text{Huynh-Feldt}}(1.21, 15.69) = 6.75, p < .02] \) and no interaction \( [F_{\text{Huynh-Feldt}}(1.21, 15.69) = .29, p > .05] \). The reversal effect demonstrated
a decrease in the number of perseverative errors for both groups from Reversals 1 to 6.

For the 5-Pair-ODR (Fig. 4D-F), the 3-year-olds learned the 5 discrimination problems as
rapidly as the 4-year-olds \( [t = 1.14, p > .05] \), and made slightly, but significantly, more total
reversal errors \([t = 3.33, p < .01]\) than the 4-year-olds. The total perseverative errors did not differ between group \([t = .003, p > .05]\). In addition, the repeated measure Age X Reversal ANOVA for reversal errors indicated no effect of Age \([F(1, 11) = 1.08, p > .05]\), a significant effect of Reversal \([F_{\text{Huynh-Feldt}}(3.89, 42.76) = 4.11, p < .01]\), and the interaction failed short of significance \([F_{\text{Huynh-Feldt}}(3.89, 42.76) = 2.29, p = .08]\). The interaction shows that the two groups differed in Reversal 4 only, with the 4-year-olds making slightly less reversal errors than the 3-year-olds \((t = 2.92, p < .02, \text{see Fig. 4E})\). For perseverative errors, neither main effects nor their interaction reached significance \([\text{Age effect: } F(1, 11) = .08, p > .05; \text{Reversal effect: } F_{\text{Huynh-Feldt}}(1.11, 12.26) = 1.85, p > .05; \text{Age X Reversal: } F_{\text{Huynh-Feldt}}(1.11, 12.26) = .05, p > .05]\).

Overall, the data indicated that, for both tasks, the 3-year-olds performed slightly, but significantly, more poorly than the 4-year-olds across the six reversals.

### 3.3 Effect of neonatal OFC and amygdala lesions on ODR performance

**1-Pair-ODR:** The acquisition, total reversal, and total perseverative errors made by all monkeys with neonatal OFC and amygdala lesions as well as the 5 control animals that were tested at both 3 months and 3 years of age are provided in Tables 3 and 4 for the 1-Pair-ODR. Repeated measure Group X Age ANOVAs on the 3 parameters revealed no significant Group effects or interactions, but a significant Age effect \([\text{Acquisition errors: } F(1, 14) = 3.75; p > .05; \text{Total reversal errors: } F(1, 14) = 39.28, p < .001; \text{Total perseverative errors: } F(1, 14) = 11.88, p < .005]\). So, as shown in Figure 5A and 5D, all groups performed slightly better at 3 years than at 3 months of age.

Reversal and perseverative errors across the 6 reversals at 3 months and 3 years were analyzed by repeated measure Group X Age X Reversal ANOVAs. For reversal errors, there
was a significant main effect of Age \([F(1, 14) = 39.28, p < .001]\) but not of Group \([F(2, 14) = 0.18, p > .05]\) or Reversal \([F(4, 14) = 1.83, p > .05]\). None of the interactions reached significance \([\text{all } ps > .05]\). Thus, as shown in Figures 5B and E, the three groups improve their performance equally from 3 months to 3 years. For the perseverative errors, the main effect of Group was not significant \([F_{\text{Huynh-Feldt}}(2, 14) = .39, p > .05]\) but the effects of Age and Reversal reached significance \([F(1, 14) = 11.31, p = .005\) and \(F_{\text{Huynh-Feldt}}(3.22, 14) = 13.31, p < .001\), respectively]. None of the interactions were significant \([\text{all } ps > .05]\). Thus, as shown in Figure 5C and F, all three groups made more perseverative errors at 3 months than at 3 years, and at both age, perseverative errors decline from the first to the sixth reversals (Bonferroni-corrected contrasts: Reversal 1 > Reversal 6, \(ps < .05\) at both 3 months and 3 years).

5-pair ODR: Table 5 provides acquisition, total reversal and total perseverative errors that each animal of Groups Neo-C/N (\(n = 9\)), Neo-Oasp (\(n = 6\)) and Neo-Aibo (\(n = 6\)) made in the 5-Pair ODR. There were no group differences for acquisition errors \([F(2, 18) = 1.27, p > .05\), see Fig. 5G\] as well as total reversal errors \([F(2, 18) = .52, p > .05]\) and total perseverative errors \([F(2, 18) = 1.72, p > .05]\).

For reversal errors, the repeated measure Group X Reversal ANOVA indicated no main effect of Group \([F(2, 18) = .52, p > .05]\) and Reversal \([F_{\text{Huynh-Feldt}}(4.16, 74.89) = 1.26, p > .05]\) but the interaction was short of significance \([F_{\text{Huynh-Feldt}}(8.32, 74.89) = 2.01, p = .054]\), indicating that performance on each reversal may differ between groups (see Fig. 5H). Planned comparisons at each reversal using Dunnett’s tests to compare each experimental group with the control group revealed that Group Neo-Oasp made more reversal errors than Group C/N in the first reversal only, although this group difference did not reach significance \((p > .05)\).
For perseverative errors, the Group X Reversal ANOVA showed no difference between Group [F(2, 18) = 1.72, p > .05], a Reversal effect that just missed significance [F_Huynh-Feldt(1.41, 25.38) = 3.54, p = .058] and no significant interaction [F_Huynh-Feldt(2.82, 25.38) = 0.74, p > .05]. Despite some apparent group differences in perseverative errors across the six reversals (Fig. 5I), these differences did not reach significance (Bonferroni corrected contrasts for Groups Neo-Aibo and Neo-Oasp separately: all ps > .05).

**Correlation analyses:** Pearson coefficient correlations were used to investigate any effects of extent of intended and unintended damage on performance of the 1-pair-ODR and 5-pair-ODR (acquisition errors, total reversal errors, and total perseverative errors). Although none of the correlations reached significance for neonatal damage to the amygdala and adjacent structures, the number of total perseverative errors in the 1-pair-ODR at 3 years correlated positively with extent of damage to area 12 [r = .814, p < .05] but not with extent of damage to areas 11, 13 or 14 [r = .447, r = -.087, r = -.573, p > .05, respectively]. All other correlations did not reach significance.

### 3.4 Comparisons between the effects of neonatal-onset versus adult-onset lesions

To assess the effects of neonatal-onset versus adult-onset OFC and amygdala lesions on the ODR tasks, performance of animals of the present study was compared to that reported for animals with adult-onset lesions tested similarly in both tasks (Kazama and Bachevalier, 2009; see Fig. 6). A summary of the statistical analyses is provided in Table 6 (see Supplement material), so that only significant differences will be reported below and the data are depicted in Figure 6.
Effects of amygdala lesions: For 1-pair-ODR, the Group (2) by Age at lesion (2) ANOVAs for acquisition errors, total reversal errors and total perseverative errors revealed only a significant Age at lesion effect \[F(1, 24) = 7.54, p < .011\] for total reversal errors. Thus, animals with both neonatal amygdala lesions and neo-sham lesions made more total reversal errors than those with late-onset lesions. The repeated measure Group (2) X Age at lesion (2) X Reversals (6) ANOVAs revealed only a significant Reversal effect for both reversal errors and perseverative errors \[F\text{Huynh-Feldt}(3.82, 91.68) = 4.85, p < .002\] and \[F\text{Huynh-Feldt}(2.91, 69.90) = 9.83, p < .001\], respectively, indicating that for all groups both error types decreased from Reversal 1 to Reversal 6.

For the 5-pair-ODR, there were no significant main effects for acquisition errors as well as for reversal and perseverative errors. The repeated measure Group (2) X Age at lesion (2) X Reversals (6) ANOVAs indicated only a significant Reversal effect for reversal errors \[F\text{Huynh-Feldt}(3.37, 60.71) = 4.43, p = .005\], indicating again that for all groups reversal errors decreased from Reversal 1 to Reversal 6.

Effects of OFC lesions: For 1-pair-ODR, a Group (2) by Age at lesion (2) revealed a significant effect only for Age at lesion for total reversal errors \[F(1, 24) = 6.83, p < .02\], indicating that animals with neonatal OFC lesions and their age-matched controls made more total reversal errors than those with late-onset lesions. There was also a significant effect of Group for total perseverative errors \[F(1, 24) = 4.67, p < .05\], but the interaction did not reach significance. Thus, overall animals with OFC lesions made slightly, but significantly, more total perseverative errors than the controls. However, post-hoc planned comparisons indicated that this group difference was significant between Groups Neo-C/N and Neo-Oasp [40 vs 108 perseverative errors, respectively, \(t = 2.49, p < .03\)], but not between Groups C and Oasp [34 vs
perseverative errors, respectively, \( t = 0.9, p > .05 \). As reported above in the correlation analyses for the neonatal lesions, the increase in perseverative errors in Group Neo-Oasp was correlated with extent of unintentional damage to area 12. Finally, the repeated measure Group (2) X Age at lesion (2) X Reversals (6) revealed a significant main effect for reversals only on perseverative errors \( [F_{\text{Huynh-Feldt}}(1.22, 29.29) = 10.17, p < .002] \), but none of the interactions were significant.

For the 5-pair-ODR, a Group (2) by Age at lesion (2) ANOVAs indicated a significant Age at lesion effect only for acquisition errors \( [F(1,18) = 4.82, p < .05] \), indicating that the Neo-groups made more errors than the Adult-groups. The repeated measure Group (2) X Age at lesion (2) X Reversals (6) ANOVAs revealed only a significant Group by Reversal interaction for reversal errors \( [F_{\text{Huynh-Feldt}}(4.4, 79.23) = 4.20, p = .003] \). Post-hoc comparisons indicated that animals with OFC lesions made slightly more reversal errors than control animals on Reversal 1, though the group difference failed short of significance (corrected \( t = 1.79, p > .05 \)).

3. DISCUSSION

The current study investigated the development of stimulus-reward and reversal learning abilities in monkeys with selective neonatal damage to either OFC areas 11 and 13 or amygdala. The results indicated that the ability to solve a single-pair discrimination problem followed by six reversals appears to be late maturing in monkeys and is relatively spared following selective lesions of either OFC areas 11/13 or amygdala. The sparing of the ability to flexibly alter responses to changes in stimulus-reward contingency was still present when the animals were tested in a more challenging object reversal task, requiring the concurrent learning and reversals of 5 discrimination problems. Finally, performance on the two reversal tasks at 3 years of age
was comparable to that reported in monkeys with the same lesions performed in adulthood, indicating that the preserved reversal learning abilities are present whether the damage to OFC areas 11/13 and amygdala occurs in infancy or in adulthood.

**4.1 Protracted development of stimulus-reward and reversal learning abilities**

The results indicated that, at 3 months of age, sham-operated control animals made three times more errors to learn a single object discrimination problem than when they were re-tested with a different discrimination problem at 3 years of age or when compared to naïve 3-year-old monkeys. Thus, our findings are in line with a previous developmental study demonstrating that 2-month-old monkeys are retarded in forming simple object-reward associations as compared to 6-month-olds (Harlow et al., 1960). Similar protracted discrimination learning was also documented in humans (Kendler and Kendler, 1970; Smiley and Weir, 1966). The poorer performance of infants in the present study cannot simply reflect poor perceptual-motor abilities given that they had a normal neurobehavioral development as measured by the Infant Neurobehavioral Assessment Scale from 1 to 16 weeks of age (K. Schauder and J. Bachevalier, unpublished data) and because they showed strong novelty preference and recognition memory in a visual paired-comparison task at 1.5 month using color pictures of different objects (Zeamer et al., 2010). Similarly, poor motivation is unlikely to be the factor affecting infants’ learning performance since the daily testing sessions occurred 12 hours after the last feeding schedule and there were very few instances during which the animals refused the food rewards during daily sessions. Alternatively, as argued by Harlow (1959), the greater error rate of infant monkeys in acquiring the simple object discrimination problem may relate instead to the use of erroneous strategies (position-habit, spatial or object alternation, etc…) and/or, more generally, to an
inability to inhibit response tendency. This later inability is exemplified by the greater number of perseverative errors, e.g. responding to the object previously rewarded during correction procedure, the monkeys made when they were 3 months of age (X ± SEM: 44.5 ± 13.7) as compared to when they were 3 years of age (9.3 ± 4.5). This inability to inhibit response tendency was also evident during performance on the reversal phase of the task.

Across the six reversals, 3-month-old control animals made more reversal and perseverative errors than when re-tested at 3 years of age (roughly seven times more at 3 months than at 3 years). These results confirmed those reported by earlier studies in monkeys (Mandell and Sackett, 2008) and humans (Kendler and Kendler, 1970; Overman et al., 1996; Smiley and Weir, 1966). There was also no evidence of improvement in performance across the six reversals, suggesting that at the young age, animals have an inability to form learning set. However, by 3 years of age, the presence of learning set was evident in all control animals. The protracted maturation of learning set ability has already been reported in both monkeys (Harlow et al., 1960) and humans (Levinson and Reese, 1967). Thus, not only do young primates have difficulty learning the stimulus-reward association of each problem, they do not easily transfer what they have learned about the task across reversals. The source of the immature performance in reversal learning is thus thought to reflect an inability to form efficient stimulus-reinforcer association learning together with an inability to making an affective shift after reinforcement contingencies have changed.

Because the animals of the present developmental study were not tested at different time points between 3 months and 3 years, the exact age at which stimulus-reward associations and reversal learning abilities reach maturity is still unknown. However, previous studies have indicated that simple object discrimination abilities reach mature levels earlier than reversal
learning abilities (Kendler and Kendler, 1970). This will suggest that the stimulus-reinforcer associations learning abilities may emerge at an earlier age than the ability to inhibit the selection of previously rewarded stimuli.

Furthermore, in contrast to previous studies that have reported that both monkey and human infant males are more proficient in reversal learning than females (Bachevalier and Hagger, 1991; Goldman et al., 1974, Overman et al., 1996), this sex difference could not be assessed in the present experiment given that we had only one male monkey in the sham-operated group. However, it is interesting to note that all but one female made more errors to acquire the 1-pair-ODR and made more reversal errors than the male. Additional studies are clearly needed to examine the progressive maturation of ODR ability between 3 months and 3 years, to establish the age at with this ability reaches adult-level of proficiency in monkeys, and to document the presence of sexual dimorphism in reversal learning.

It is interesting to note that performance of animals in all three groups tested at 3.5 years of age was slightly but significantly poorer than at 5-years of age (see Figure 6). There are several possible explanations for this small age difference. The first one relates to prior training experience before the ODR tasks. Whereas the 3.5-year-olds did not have experience with any problem-solving tasks prior to reversal learning, the 4.5-year-olds had received training in a concurrent visual discrimination and devaluation task. The second may be associated with variation in genetic background of the two populations of monkeys, since they came from different breeding colonies. The third may correspond to different rearing conditions in the two groups given that animals of the present studies were nursery-reared, whereas the 4.5-year-olds were mother-reared. Finally, it remains possible that the age difference could still indicate some
maturational processes given that the prefrontal cortex continues to mature until 4-5 years of age in monkeys (Knickmeyer et al., 2010).

4.2 Preserved stimulus-reward and reversal learning after neonatal OFC areas 11/13 and amygdala lesions

The protracted development of reversal learning performance has been thought to reflect the prolonged development of the prefrontal cortex, and more specifically the OFC (Clarke et al., 2004; Goldman et al., 1983). However, the present findings demonstrate for the first time that OFC areas 11/13 do not seem to be the critical source of this protracted development (see section 4.2, below).

Monkeys that had received neonatal OFC areas 11/13 lesions performed similarly to sham-operated controls at both ages and across both reversal tasks. They demonstrated a sharp improvement in performance between 3 months and 3 years in their ability to form stimulus-reward associations and in reversal learning, and performed normally in the more difficult 5-pair ODR task. The present findings contrast with those reported by Miller and colleagues (1971). In this earlier study, damage to extensive regions of the OFC at 1-2 months of age yielded severe reversal learning deficits when the monkeys were tested at 1-1.5 year of age. The divergent results between the two studies may have resulted from the role of experience in learning performance given that, unlike the earlier study, our animals were given a test and re-test on the same task at two different ages. However, there are several reasons suggesting that experience have had little influence on the improvement in ODR performance. First, the control monkeys that were tested for the first time in the 1-pair-ODR at 3 years performed as well as those that have had prior training with the task at 3 months. In addition, the neonatal orbital frontal lesions
did not impact performance on the 5-pair-ODR that was given for the first time at 3 years of age. Second, Goldman (1976) has directly assessed the role of experience on recovery of functions following neonatal orbital lesions and found significant improvement in performance during the re-test of the animals. Nevertheless, despite this improvement, the animals with the neonatal lesions were still impaired as compared to controls.

Another obvious difference between the two studies relates to the extent of the OFC lesions, which in the case of the earlier studies included not only areas 11/13, but also OFC area 10 anteriorly, area 12 laterally, and area 14 more medially. This difference in the effects of extent of OFC lesions on reversal learning is reminiscent with a similar difference reported in adult-onset lesions. Thus, as for the neonatal OFC lesions, when adult-onset OFC lesions were restricted to areas 11/13 or area 14 no reversal learning deficit was found (Kazama and Bachevalier, 2009; Ruddebeck and Murray, 2011;) as compared to the severe deficits reported after extensive OFC lesions (Butter, 1969; Dias et al., 1996; Izquierdo et al., 2004; Meunier et al., 1997; Mishkin, 1964, Walton et al., 2010).

Given that reversal learning scores in both the 1-pair ODR and 5-pair ODR of the animals with neonatal OFC lesions at 3 years of age did not differ from that of monkeys that had received the same OFC lesions in adulthood and that were tested in exactly the same way (Kazama and Bachevalier, 2009), it is likely that the difference between the results of the earlier report (Miller et al., 1971) and those reported here is due to OFC lesion extent.

Given the severe reversal learning impairment following large OFC lesions, the critical question that remains to be addressed now is which specific area(s) within the OFC mediates reversal learning? As suggested by subregional OFC lesions in adult monkeys, deficits in reversal learning are more apparent when OFC damage involves lateral area 12 rather than more
medial OFC areas 11/13 or 14 (Butter, 1969; Dias et al., 1996; Iversen and Mishkin, 1970; Kazama and Bachevalier, 2009; Ruddebeck and Murray, 2011; Rygula et al., 2010). Thus, a likely candidate for further investigations will be the ventrolateral prefrontal (area 12) in monkeys. Impaired ODR performance after damage to area 12 is known to result from an increase in perseverative errors, indicative of an inability to withhold responding to negative stimuli (Iversen and Mishkin, 1970). In line with this interpretation, it is interesting to note that the slight but significant increase in total perseverative errors in the 1-pair-ODR at 3 years in animals with Neo-Oasp was in fact correlated with the extent of damage to area 12. Finally, several human neuroimaging studies have demonstrated increased activity in area 12 while subjects are engaged in reversal tasks (Budhani et al., 2007; Cools et al., 2002; Mitchell et al., 2008; O’Doherty et al., 2003; Remijnse et al., 2005).

Finally, a similar pattern of results was found after neonatal amygdala lesions. Thus, infant monkeys with these lesions improved their performance on the 1-pair ODR task from 3 months to 3 years of age as did the sham-operated controls, and performed normally on the 5-pair ODR task. In fact, their performance at 3 years of age was similar to that of adult animals that had received the same amygdala lesions in adulthood (Kazama and Bachevalier, 2009). Thus, neither the OFC areas 11/13 nor the amygdala are critical for the maturation of reversal learning abilities in monkeys.

Although the results suggest that OFC lesions limited to areas 11/13 and selective amygdala lesions preserving fibers of passage spared reversal learning abilities, it is important to consider whether the lack of impairment following these neonatal lesions could in any way have resulted from brain plasticity. Recovery of functions following early brain lesions has been reported since the early 1940s (Kennard, 1940, 1942) and recent research in rodents have shown
that neonatal damage to the OFC produces virtually no chronic cognitive or motor deficits (Kolb et al., 2004). However, we believe that this alternative explanation is improbable given that, despite their preserved reversal learning abilities, animals with neonatal OFC areas 11/13 and amygdala lesions were impaired in other behavioral tasks for which the same lesions yielded significant deficits with adult-onset lesions. Thus, as for the adults (Machado and Bachevalier, 2007a, b, 2008), both the neonatal OFC and amygdala lesions did severely impact the animals’ ability to modulate emotional reactivity according to threat levels provided by a Human Intruder (Raper et al., 2009, 2010) and to modulate their choice selection when reward values of stimuli have changed (Kazama et al., 2007). All together the data suggest that both in infancy and in adulthood OFC areas 11/13 and the amygdala are not critical for reversal learning abilities.

4.3 Conclusions

In summary, the present findings inform our understanding of the development of stimulus-reinforcer associations and reversal learning and their neural substrates. The protracted maturation of reversal learning abilities in nonhuman primates was believed to depend on the delayed development of the OFC (Goldman et al., 1971). We now show that the subregion of the OFC that plays a critical role in the maturation of reversal learning abilities is not its lateral sector, i.e. areas 11 and 13. We also show that, despite its putative role in adjusting choice behavior with changing stimulus-value associations both in adulthood (Bachevalier et al., 2011; Izquierdo et al., 2004; Machado and Bachevalier, 2007a, b) and during development (Bachevalier et al., 2011; Kazama et al., 2007), OFC areas 11 and 13 are not necessary for the modulation of behavior when reinforcement contingencies have changed. Given that reversal learning can be divided in several cognitive processes, such as learning associations between
neutral stimuli and their rewarding or punishing value, switching to new associations (inhibiting
the selection of the previously rewarded stimulus in favor of the newly rewarded stimulus after
contingencies have reversed), and forming learning-sets to improve performance, it is quite
possible that several of these processes rely upon distinct sectors of the OFC (Butter, 1969;
Iversen and Mishkin, 1970; see for review Roberts, 2006). Such a proposal is consistent with
recent functional neuroimaging studies that have identified multiple regions of activation within
OFC specifically linked to reversal learning abilities (Budhani et al., 2007; Cools et al., 2002;
Kringelbach and Rolls, 2003; Mitchell et al., 2008; O’Doherty et al., 2003; Remijnse et al.,
2005).

Finally, the sparing of reversal learning after neonatal OFC lesions is clinically relevant
given that the ODR has been the benchmark task to investigate functioning of the OFC in
populations of human subjects in which dysfunction of the OFC is suspected, i.e. schizophrenia,
obsessive–compulsive disorder, ADHD, autism, depression and sociopathies (see for review
Bachevalier and Loveland, 2006; Blair, 2004; Chamberlain et al., 2005; Fernando and Robbins,
2011; Gorwood, 2008; Moghaddam and Homayoun, 2008). The current data indicate the need to
design additional studies to better understand the specific functions mediated by different OFC
subregions and their development as well as to investigate whether different forms of atypical
development may be in fact associated with dysfunction of different OFC sectors.
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Figure Legends

**Figure 1:** Intended orbital frontal lesion and extent of lesions in a representative case (Neo-Oasp-4). Intended damage is shown in gray on coronal sections through the orbital frontal cortex of an infant macaque brain atlas (left column) and matched coronal MR images are shown through the OFC lesion in case Neo-Oasp-4 (middle column). The lack of gray matter on the ventral surface indicates where cortical tissue has been aspirated. The estimated lesion extent is reconstructed on the right column. Arrows point to areas of sparing. Abbreviations: mos – medial orbital sulcus; los – lateral orbital sulcus; numbers refer to Brodmann areas (Brodmann, 1909).

**Figure 2:** Intended amygdala lesion and extent of damage in a representative case (Neo-Aibo-1). Intended damage is shown in gray on coronal sections through the anterior-posterior extent of the amygdala of an infant macaque brain atlas (left column). Hypersignals caused by edema resulting from cell death are shown in matched FLAIR MR images (middle column), and extent of damage is reconstructed on corresponding drawing of coronal sections of a normal brain (right column). Asterisks point to areas of unintended damage to the ventral striatum and the anterior hippocampus on the left (see levels +5 to +3, respectively). Arrows indicate slight sparing of tissue within the ventral amygdala mostly on the left. Abbreviations: A – amygdala; amts – anterior medial temporal sulcus; ERh – entorhinal cortex; H – hippocampus; ls – lateral sulcus; ots – occipital temporal sulcus; PRh – perirhinal cortex; rs – rhinal sulcus; sts – superior temporal sulcus; TE, temporal cortical area and TH/TF – cytoarchitectonic fields of the parahippocampal gyrus as defined by von Bonin and Bailey (1947).
**Figure 3:** 1-Pair ODR – Scores are mean errors made prior to reaching acquisition criterion (A) and mean reversal (B) and perseverative (C) errors for each reversal at 3 months and 3 years for the 5 control animals (Group Neo-C/N) that were tested at both ages. Asterisks indicate $p < .05$.

**Figure 4:** 1-pair vs 5-pair-ODR – Scores are mean acquisition errors made prior to reaching criterion in 1-Pair-ODR (A) and 5-Pair-ODR (D) for control animals tested at 3 years (open bars) and those tested at 4 years of age (hatched bars, data are from Kazama and Bachevalier, 2009). Mean reversal errors for each reversal in 1-Pair-ODR (B) and 5-Pair-ODR (E) and mean perseverative errors for each reversal in 1-Pair-ODR (C) and for 5-Pair-ODR (F) at 3 years (filled diamonds) and 4 years (filled circles). Asterisks indicate $p < .05$.

**Figure 5:** Neonatal orbital and amygdala lesions – Scores are mean acquisition errors made prior to reaching criterion in 1-Pair-ODR at 3 months (A) and 3 years (D) and in 5-Pair-ODR (G). Mean reversal errors for each reversal in 1-Pair-ODR at 3 months (B) and 3 years (E), and in 5-Pair-ODR (H). Mean perseverative errors for each reversal in 1-Pair-ODR at 3 months (C) and 3 years (F) and in 5-Pair-ODR (I). Neo-C/N: animals with sham-operations or no operations (white bars and diamond with dotted lines); Neo-Aibo: animals with neonatal amygdala lesions (light gray bars and squares with solid lines); Neo-Oasp: animals with OFC Areas 11 and 13 lesions (dark gray bars and triangles with solid lines).

**Figure 6:** Early-onset vs late-onset lesions – Scores are mean errors made prior to reaching criterion during acquisition and mean total reversal errors for 1-Pair-ODR (A,B) and for 5-Pair-
ODR (C,D, respectively). Solid bars represent animals with neonatal lesions, i.e. sham lesions (Neo-C/N: white bars), neonatal amygdala lesions (Neo-Aibo, light gray bars), and neonatal orbital frontal lesions (Neo-Oasp, dark gray bars). Hatched bars indicate animals with adult-onset sham lesions (Adult-C: white hatched bars), amygdala lesions (Adult-Aibo, light gray hatched bars), and orbital frontal lesions (Adult-O, dark gray hatched bars). All Neo-Groups received their operations at 7-10 days of age and were tested at 3.5 years of age (Neo-3-years), whereas all Adult-Groups received their operations around 3.5 years of age and were tested at 4.5 - 5 years of age (Adult-4-years). Data from the adult groups are from Kazama and Bachevalier, 2009.
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Walton, ME, Behrens, TEJ, Buckley, MJ, Rudebeck, PH, Rushworth, MFS (2010)


Table 1. Extent of intended and unintended damage in Group Neo-Oasp

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Data are the estimated percentage of damage as assessed from MR (post-surgical T1) images. L: percentage of damage to the left hemisphere; R: percentage of damage to the right hemisphere; Avg: average of L and R; W = (L x R)/100 [weighted index as defined by Hodos and Bobko (1984)]; X: group mean. Areas 11, 12, 13, and 14: cytoarchitectonic subregions of the macaque frontal lobe and Ia: agranular insular areas as defined by Carmichael and Price (1994).
Table 2: Extent of intended and unintended damage in Group Neo-Aibo

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Data are the estimated percentage of damage as assessed from MR (post-surgical FLAIR) images. Abbreviations as in Table 1.
Table 3: 3-Month 1-pair ODR Task

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Scores are total number of errors made before criterion days for the acquisition (Acq) and each of the six reversals (Rev 1 to Rev 6) as well as Total Reversal Errors and Total Perseverative Errors across the six reversals.
Table 4: 3-Year 1-pair ODR Task

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</table>

Scores are total number of errors made before criterion days for the acquisition (Acq) and each of the six reversals (Rev 1 to Rev 6) as well as Total Reversal Errors and Total Perseverative Errors across the six reversals. In addition to average of the 9 animals in Group C/N, the table provides separate mean for the 5 animals that had been tested on the 1-pair-ODR at 3 months of age and for the 4 animals that were tested for the first time at 3 years of age (as indicated by the asterisks).
Table 5: 3-Year 5-pair ODR Task

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<thead>
<tr>
<th>Sex</th>
<th>Cases</th>
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<th>Rev 2</th>
<th>Rev 3</th>
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</table>

Scores are total number of errors made before criterion days for the acquisition (Acq) and each of the six reversals (Rev 1 to Rev 6) as well as Total Reversal Errors and Total Perseverative Errors across the six reversals. Separate averages for Group Neo-C/N are indicated by parentheses. Asterisks indicate animals that did not have prior experience with 1-Pair ODR at 3-months of age.
The table below illustrates the effects of early-onset versus late-onset lesions on 1-pair-ODR and 5-pair-ODR for both control vs. amygdala lesions and control vs OFC lesions.

<table>
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<tr>
<th>Control vs Amygdala lesions</th>
<th>1-Pair-ODR</th>
<th>5-Pair-ODR</th>
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<td><strong>Acquisition errors</strong></td>
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<td>Group</td>
<td>F(1, 24) = 1.55, ns</td>
<td>F(1, 18) = 1.29, ns</td>
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<tr>
<td>Age at Lesion</td>
<td>F(1, 24) = 1.10, ns</td>
<td>F(1, 18) = 3.85, p = .065</td>
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<tr>
<td>Interaction</td>
<td>F(1, 24) = .002, ns</td>
<td>F(1, 18) = .35, ns</td>
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<tr>
<td><strong>Total reversal errors</strong></td>
<td>F(1, 24) = .32, ns</td>
<td>F(1, 18) = .17, ns</td>
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<tr>
<td>Group</td>
<td>F(1, 24) = 7.54, p = .01</td>
<td>F(1, 18) = 2.32, ns</td>
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<td>Age at Lesion</td>
<td>F(1, 24) = .59, ns</td>
<td>F(1, 18) = .03, ns</td>
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<td>Interaction</td>
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<td>F(1, 18) = .12, ns</td>
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<td><strong>Total perseverative errors</strong></td>
<td>F(1, 24) = 1.70, ns</td>
<td>F(1, 18) = .57, ns</td>
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<td>Group</td>
<td>F(1, 24) = 2.27, ns</td>
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<td>Age at Lesion</td>
<td>F(1, 24) = 2.27, ns</td>
<td>F(1, 18) = .12, ns</td>
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<tr>
<td><strong>Reversal errors across 6 reversals</strong></td>
<td>F(1, 24) = 3.23, ns</td>
<td>F(1, 18) = .17, ns</td>
</tr>
<tr>
<td>Group</td>
<td>F(1, 24) = 7.54, p = .01</td>
<td>F(1, 18) = 2.32, ns</td>
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<td>F(1, 18) = .03, ns</td>
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<td>F(1, 18) = 1.05, ns</td>
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<td>F(1, 18) = 2.36, p = .074</td>
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<td>F(1, 18) = 1.25, ns</td>
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<td><strong>Perseverative errors across 6 reversals</strong></td>
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<td>F(1, 18) = 4.82, p &lt; .05</td>
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<td>F(1, 24) = .007, ns</td>
<td>F(1, 18) = .33, ns</td>
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<td>F(1, 18) = .64, ns</td>
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<td>F(1, 24) = 6.83, p &lt; .02</td>
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<td>Age at Lesion</td>
<td>F(1, 24) = .46, ns</td>
<td>F(1, 18) = 1.14, ns</td>
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<td>F(1, 18) = .31, ns</td>
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<td>F(1, 24) = .37, ns</td>
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<td>Age at Lesion</td>
<td>F(1, 24) = .37, ns</td>
<td>F(1, 18) = 1.54, ns</td>
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<td><strong>Reversal errors across 6 reversals</strong></td>
<td>F(1, 24) = .54, ns</td>
<td>F(1, 18) = .639, ns</td>
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<tr>
<td>Group</td>
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<td>F(1, 24) = .26, ns</td>
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<td>Group X Reversal</td>
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<td>Group X Age at Lesion</td>
<td>F(1, 24) = 2.08, ns</td>
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<td>Age at Lesion</td>
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<td>F(1, 24) = 10.17, p &lt; .002</td>
<td>F(1, 18) = 2.38, ns</td>
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*Note: F values with p < .05 are highlighted.*
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<th>Intended Lesion Extent</th>
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<th>Reconstructed Lesion Extent</th>
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</tr>
</tbody>
</table>
Figure 3

A. Acquisition Errors

B. Reversal Errors

C. Perseverative Errors
Figure 5
Click here to download high resolution image
Figure 6

1-Pair ODR
Neo 3-Years

A.

Acquisition Errors

3-4 Years of Age

Neo-C/N  Adult-C  Neo-Aibo  Adult-Aibo  Neo-Oasp  Adult-O

5-Pair ODR
Adult 4-Years

C.

Acquisition Errors

3-4 Years of Age

Neo-C/N  Adult-C  Neo-Aibo  Adult-Aibo  Neo-Oasp  Adult-O

B.

Total Rev. Errors

3-4 Years of Age

Neo-C/N  Adult-C  Neo-Aibo  Adult-Aibo  Neo-Oasp  Adult-O

D.

Total Rev. Errors

3-4 Years of Age

Neo-C/N  Adult-C  Neo-Aibo  Adult-Aibo  Neo-Oasp  Adult-O
Figure 4

1-Pair ODR

Acquisition Errors

A.

Errors

30
20
10
0

Neo-C/N 3-Years
Adult-C 4-Years

B.

Errors

100
80
60
40
20
0

Group Neo-C/N (3-Years)
Group C (4-Years)

Reversal Errors

C.

Errors

40
20
0

Group Neo-C/N (3-Years)
Group C (4-Years)

5-Pair ODR

D.

Errors

30
20
10
0

Neo-C/N 3-Years
Adult-C 4-Years

E.

Errors

100
80
60
40
0

Group Neo-C/N (3-Years)
Group C (4-Years)

Reversal Perseverative Errors

C.

Errors

40
20
0

Group Neo-C/N (3-Years)
Group C (4-Years)

F.

Errors

40
20
0

Group Neo-C/N (3-Years)
Group C (4-Years)